IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No.	:	10/085,539	Confirmation No.:	9853
Applicant	:	CARLYLE, Wenda, et al.		
Filed	:	February 26, 2002		
TC/A.U.	:	1616		
Examiner	:	WEBMAN, Edward J.		
Docket No.	:	P872		
Customer No.	:	28390		
Title	:	PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA LIGAND ELUTING MEDICAL DEVICE		

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ROBERT L. CAFFERATA UNDER 37 CFR § 1.131

I, ROBERT L. CAFFERATA, declare the following:

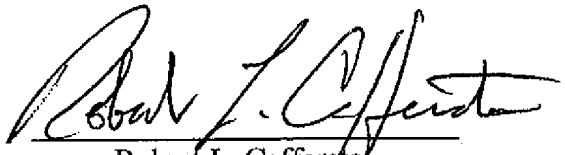
1. I previously was employed by MEDTRONIC, INC., and am one of the inventors of the above-identified application.

2. I understand that in an Office Action dated 14 April 2007, the Examiner rejected Claims 1, 2, 5-7, 9, 11, and 27, of the above-identified application under 35 U.S.C. §103(a) as obvious over the combination of U.S. Patent No. 5,443,458 and International Publication No. WO 01/07066.

3. I understand that International Publication No. WO 01/07066 was filed on 19 July 2000 and published on 1 February 2001. The cover page of International Publication No. WO 01/07066 is attached as EXHIBIT A.

4. Two of my redacted laboratory notebook pages, which were prepared in the United States and witnessed by Wenda Carlyle before 1 February 2001, are attached as EXHIBIT B. The laboratory notebook pages summarize and evidence the reduction to practice of the subject matter claimed in the above-identified application. Specifically, EXHIBIT B, page 1, paragraph 1, describes a stent designed to improve the treatment of restenosis by eluting ligands of peroxisome proliferator-activated receptor gamma (PPARγ) from the stent. EXHIBIT B, page 1, paragraphs 2 and 6, and page 2, paragraph 1, disclose that rosiglitazone is a PPARγ ligand and is of particular interest to elute from a stent to treat restenosis.

6. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of this application or any patents issuing thereon.



12-18-07

Robert L. Cafferata
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Date

EXHIBIT A

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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1 February 2001 (01.02.2001)

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(10) International Publication Number
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9917405.4 23 July 1999 (23.07.1999) GB

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(72) Inventors; and

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/07066 A2

(54) Title: METHODS OF TREATMENT AND DRUG SCREENING METHODS

(57) Abstract: A method of preventing or reducing foam cell development from macrophages, or removing foam cells, in a patient, the method comprising administering to the patient an effective amount of an inhibitor of PPARδ activity. A method of preventing or treating a vascular disease associated with plaque formation and/or thrombotic blockage of the blood vessels in a patient, the method comprising administering to the patient an effective amount of an inhibitor of PPARδ activity.

EXHIBIT B

[INVENTION]: I DISCLOSE A MODIFICATION TO A STENT DESIGNED TO IMPROVE THE TREATMENT OF RESTENOSIS BY ELUTING LIGANDS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPARγ) FROM THE STENT. IN ITS SIMPLEST EMBODIMENT, A SINGLE PPARγ LIGAND IS ADDED TO A STENT BEFORE IMPLANTATION IN A PHARMACEUTICALLY SUFFICIENT DOSE & WITH SUFFICIENT DURATION OF ELUTION TO BLOCK THE LOCAL NEOPLASIA OF RESTENOSIS AFTER STENT DEPLOYMENT IN THE BODY.

RATIONALE FOR CHOOSING PPARγ LIGANDS: PPARγ IS A MEMBER OF A NUCLEAR RECEPTOR SUPERFAMILY THAT IS ACTIVATED BY BINDING CERTAIN LIGANDS. THESE LIGANDS CAN BE OBTAIN FROM CERTAIN FATTY ACIDS, EICOSANOIDS AND INSULIN-SENSITIZING THIAZOLIDINEDIONES. SEVERAL PHARMACEUTICAL DRUGS ARE PART OF THE LATTER CLASS: ROSIGLITAZONE, PIOGLITAZONE & TROGLITAZONE.

AN IMPORTANT CHARACTERISTIC OF ANTI-RESTENOTIC DRUGS AGENTS IS THEIR ABILITY TO INHIBIT SMOOTH MUSCLE CELL (SMC) PROLIFERATION. PPARγ LIGANDS ARE KNOWN TO INHIBIT VASCULAR SMC PROLIFERATION PROBABLY BY DIRECT INHIBITION OF CYCLIN-DEPENDENT KINASES (1, 2).

SECOND PROPERTY KEY IN AN ANTI-RESTENOTIC AGENT IS INHIBITION OF SMC MIGRATION (i.e. FROM THE MEDIA TO THE NEOINTIMA OF AN ARTERY). PPARγ LIGANDS BLOCK MIGRATION OF VASCULAR SMCs (1).

THIRD PROPERTY FOR AN ANTI-RESTENOTIC AGENT IS ITS ABILITY TO BLOCK LOCAL INVASION/ACTIVATION OF MONOCYTES &/OR THEIR RELEASING SECRETION OF GROWTH FACTORS/CYTOKINES WHICH PRESUMABLY TRIGGER SMC ENTRY INTO THE CELL CYCLE. PPARγ AGONISTS INHIBIT ACTIVATION OF MONOCYTES (3) & CYTOKINES PRODUCTION BY MONOCYTES (3). INTERESTINGLY, IT IS KNOWN THAT CERTAIN NON-STEROIDAL ANTI-INFLAMMANT DRUGS (NSAIDs) LIKE SULINDAC ARE ANTI-RESTENOTIC IN PIGS WITH PLAQUE-LIKE LESIONS (4). THIS COULD BE RELATED TO THE FACT THAT NSAIDs HAVE PPARγ AGONIST ACTIVITY AT HIGH CONCENTRATIONS (5).

RECENT CLINICAL FINDINGS DEMONSTRATE THAT PATIENTS DOSED SYSTEMICALLY WITH TROGLITAZONE HAVE REDUCED NEOINTIMAL PROLIFERATION AT SIX-MONTHS AFTER CORONARY STENT IMPLANTATION (6). UNFORTUNATELY THIS DRUG, UNDER THE TRADE NAME REZULIN IS RECENTLY WITHDRAWN FROM USE IN TREATING TYPE II DIABETICS BECAUSE OF EXCESSIVE LIVER TOXICITY. SINCE PLASMA DRUG LEVELS WERE SIMILAR IN BOTH CASES, IT IS LIKELY THAT THE ANTI-RESTENOTIC EFFECTS OF SYSTEMIC TROGLITAZONE COULD ALSO LEAD TO

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Witnessed & Understood by me.

Invented by ROBERT L. CAFFERATA

Read by

DEATHS FROM LIVER TOXICITY. ONE OF THE PURPOSES OF THE PRESENT INVENTION IS TO REDUCE THE DOSE & BIODISTRIBUTION OF THIS DRUG BY ELUTING IT LOCALLY FROM A STENT WITHIN THE BODY LUMEN BEING TREATED FOR RESTENOSIS.

METHODS FOR COMBINING PHARMACEUTICAL DOSAGE FORMS ONTO IMPLANTABLE DEVICES STENTS:

- PRECIPITATION, COACERVATION, CRYSTALLIZATION OF DRUG ONTO THE SURFACE OF STENT (OR WELLS/CHANNELS PLACED IN THE BODY OF THE STENT AS DRUG RESERVOIRS)
- BLENDING WITH POLYMERS THAT COAT THE SURFACES OF THE STENT (& ITS CHANNELS) & ACT AS A DIFFUSION-BARRIER TO CONTROL RELEASE OF DRUG
- ADDITION TO THE MATERIAL USED TO COMPOUND ERODIBLE POLYMERIC STENTS.
- CONTACT WITH CHEMICALLY REACTIVE SURFACES (FILMS) BONDED TO THE SURFACE OF THE STENT. ONE SUCH EXAMPLE WAS ANTICIPATED IN RAPID IN-SITU RELEASING "DRUG IMPLANT (pp 7-11).

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Witnessed & Understood by me,

Invented by ROBERT L. CAPPUCCITTI

Recorded by

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